VERIFICATION OF TRANSLATION

I, Melissa Stanford, a translator with Chillson Translating Service, 3530 Chas Drive, Hampstead, Maryland, 21074, hereby declare as follows:

That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application 197 24 230.8 titled, "Stents with a Radioactive Coating, Processes for their Production and their Use for Restenosis Prophylaxis"
filed with the German Patent Office on June 3, 1997;

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

And further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any registration resulting therefrom.

By Melissa Stanford

Executed this 11 day of Oct 1999.

Witness Anne Chillson

Translator's Notes:

In Example 13a, the last sentence presumably has a verb missing. From the context of the preceding sentence, this verb would appear to be "washed," and thus "washed" was inserted in brackets in the English translation (page 28, line 2).

There is presumably a word missing in the title of Example 21, and the word is probably "mittels [using]" before "elektrochemischer Reduktion [electrochemical reduction]," as it appears in the title of Example 20.

Two **identical** copies of Figure 1 (Galvanisierzelle = Galvanization Cell) appear at the end of the German text, so only one English translation is provided.

FEDERAL REPUBLIC OF GERMANY

Certificate

The SCHERING AKTIENGESELLSCHAFT, Berlin/Germany filed a patent application under the designation

"Stents with a Radioactive Coating,
Processes for their Production and their Use for
Restenosis Prophylaxis"

with the German Patent Office on June 3, 1997 and declares that it claims the internal priority of the application in the Federal Republic of Germany of April 30, 1997, File number 197 18 340.9.

The attached copies are a true and accurate rendition of the original document of this patent application.

In the German Patent Office the application has provisionally received the symbols A 61 M, A 61 F and A 61 L of the International Patent Classification.

[Seal]

Munich, July 13, 1998

For the Director of the German Patent Office

/s/

Agurks

File No.: 197 24 230.8

Stents with a Radioactive Coating, Processes for their Production and their Use for Restenosis Prophylaxis

The invention relates to stents that are radioactively coated on the surface by means of adhesives, processes for their production and their use for restenosis prophylaxis.

Prior Art

Radioactive stents are prior art (EP 0433011, WO 94/26205, US 5176617). Stents are endoprostheses that make it possible to keep open duct-like structures in the bodies of humans or animals (e.g., vascular, esophageal, tracheal and bile duct stents). They are used as palliative measures in the case of stenoses by obstruction (e.g., arteriosclerosis) or external pressure (e.g., in the case of tumors). Radioactive stents are used, for example, after vascular-surgery interventions or radiological interventions (e.g., balloon angioplasty) for restenosis prophylaxis. Such radioactive stents can be produced, for example, by activation of a non-radioactive stent using irradiation with protons or deuterons from a cyclotron (WO 94/26205).

There is now the problem that, on the one hand, generally no cyclotron is available at the site of the use of the stent to

undertake an activation of the stent, and, on the other hand, the activated stent cannot be stored indefinitely or transported in any arbitrary way due to the sometimes short half-life of the activated isotope and for reasons of protection against radiation.

The object of this invention is therefore to make available stents that can be activated independently by a cyclotron. In particular, the object of the invention is to make available stents that can be coated independently by a cyclotron with a preselected radioactive isotope.

This object is achieved by the stents that are described below, as they are characterized in the claims.

D scription of the Invention

The above-described object is achieved according to the invention in that the radioactive isotope is secured to the surface of the stent by means of an adhesive.

The device according to the invention thus consists of the metal parent substance of the stent, an adhesive on the surface of the stent and an adhesive radioactive isotope.

As a parent substance, the commercially available vascular implants can be used, e.g., a Wiktor stent, a Strecker stent or a Palmaz-Schatz stent.

As adhesives, peptides, fats or gold in combination with a thiol-group-containing complexing agent are used.

It is thus possible, for example, to use modified polyurethanes that in turn contain complexing agents.

As adhesives, however, peptides can also be used that on the one hand carry a complexing agent and on the other hand bind specifically to the metal of the stent. Examples of these compounds are labeled endothelin derivatives, as they are described in, e.g., EP 606683, DE 4425778, DE 43 37 600, DE 4337599 and DE 19652374 (e.g., Tc-99m-Asp-Gly-Gly-Cys-Gly-Cys-Phe-(Dr-Trp)-Leu-Asp-Ile-Ile-Trp).

As adhesives, fats that carry a complexing agent can also be used. Examples of this are the complexing agents that carry lipophilic radicals and that are mentioned in DE 43 40 809, EP 450742, EP 438206, EP 413405 or WO 96/26182.

Moreover, gold in combination with a thiol-group-containing complexing agent can also be used as an adhesive. It is known that thiol-group-containing compounds show an increased affinity to gold-coated surfaces (H. Schönherr et al. J. Am. Chem. Soc. 118 (1996), 13051-13057). Surprisingly enough, elementary gold that is on the surface of the stent is also able to secure specific complexing agents, if they have thiol groups. The complexing agents in turn secure the radioactive isotopes.

For the purposes of this document, complexing agents are, e.g., DTPA, DOTA, DO3A, EDTA, TTHA, MAG_2-amides, MAG_3-amides and derivatives thereof.

As radioactive isotopes, the radioactive isotopes of elements Ag, Au, Ba, Bi, C, Co, Cr, Cu, Fe, Gd, Hg, Ho, In, Ir, Lu, Mn, Ni, P, Pb, Pd, Pm, Pt, Re, Rh, Ru, S, Sb, Sc, Sm, Tb, Tc or Y can be used.

The invention therefore relates to radioactive stents, characterized in that the radioactive isotope is secured to the surface of the stent by means of an adhesive.

The stents according to the invention can be produced as follows by way of example:

1. Peptide as an adhesive

1.1 First, a peptide is selected that for its part is able to complex heavy metal ions. The latter is activated by reaction with the radioactive isotope (e.g., ^{186}Re or ^{188}Re) optionally together with a reducing agent. The radiolabled peptide is dissolved in a solvent (e.g., water, phosphate buffer), and the stent is immersed in the peptide solution. After the stent is removed from the peptide solution, it is dried in a drying chamber at room temperature. After the stent is washed, the latter is ready for use.

1.2 In a variant of the process, the uncoated stent is first coated with the non-activated peptide. The thus coated stent is then immersed in a solution that contains the radioactive metal (e.g., ^{186}Re or ^{188}Re) optionally together with a reducing agent (e.g., $SnCl_2$) and thus is charged with this isotope. After the stent is washed, the latter is ready for use.

2. Fat as an adhesive

2.1 An uncoated stent is first coated with a lipophilic compound (e.g., 3,9-bis(carboxymethyl)-6-bis(octadecyl)-aminocarbonylmethyl-3,6,9-triazaundecanedioic acid, WO 96/26182) as an adhesive. This lipophilic compound carries a DTPA radical as a complexing agent. The stent can be directly immersed in the compound or a solution thereof. After the stent is coated with the compound, it is mixed with a solution of the radioactive metal (e.g. $^{90}YCl_3$). After the stent is washed, the latter is ready for use.

2.2 In a variant of this process, the coating of the stent is carried out in two stages. In this regard, the stent is first treated with a lipophilic compound that carries amino groups. The amino groups are then reacted with DTPA-monoanhydride, as it is described in the literature. The stent now has a coating that carries the complexing agents (here: DTPA). The stent that is coated in this way is then mixed with a solution of radioactive metal (e.g. $^{90}YCl_3$). After the stent is washed, the latter is ready for use.

3. Gold/thiol-group-containing complexing agents as adhesives

3.1. An uncoated stent is first coated electrochemically with elementary gold (by internal electrolysis, cementation). The gold-coated stent is then immersed in an aqueous solution of a thiol-group-containing complexing agent (e.g., N,N-dimethyl-2-(3,3,5,11,13,13-hexamethyl-1,2-dithia-5,8,11-triazacyclotridecan-8-yl)-ethylamine or the coupling product of 11-amino-undecyl-1-thiol with DTPA-bis-anhydride). The thiol-group-containing complexing agent adheres to the gold-coated stent. The stent that is prepared in such a way is now mixed with a solution of the radioactive metal (e.g., $^{67}CuSO_4$). After the stent is washed, the latter is ready for use. The complexing agent can be synthesized on the surface of the stent. It is possible to apply first only one component of the complexing agent to the gold-coated stent and then to couple this component with additional partial units. This procedure is described in detail in the examples.

3.2 In a variant of this process, the gold-coated stent is mixed with a solution of the thiol-group-containing complexing agent, which for its part already complexes a radioactive isotope. After the stent is washed, the latter is ready for use.

3.3 In a variant of this process, the gold-coated stent is mixed with a solution of the thiol-group-containing

compound, which in turn contains ^{35}S. After the stent is washed, the latter is ready for use.

3.4 In another variant of this process, the gold-coated stent is mixed with a solution of the thiol-group-containing complexing agent, whereby the thiol group is labeled with ^{35}S, and the complexing agent already complexes a radioactive isotope (e.g., ^{67}Cu). After the stent is washed, the latter is ready for use.

Within the framework of this application, the notations ^{nn}X and X-nn (X: element symbol, nn: mass number) are to be regarded as synonymous for radioactive isotopes (Example: ^{110}Ag corresponds to Ag-110).

The above-described processes are generally performed at temperatures of 0-100°C. In the coating of the stent with the adhesive, solvents can be used on the basis of the respective adhesive. When a non-aqueous solvent is used, the latter is to be removed before the implantation.

The stents can also be coated with two or more different isotopes. It is possible in particular to apply short-lived and long-lived isotopes together on a stent (for example, ^{55}Co with ^{55}Fe, ^{35}S with ^{67}Cu or ^{99}Mo with ^{57}Co).

The operations that are necessary for implementing the above process that is described in principle are known to one skilled in the art. Special embodiments are described in detail in the examples.

The stents according to the invention achieve the above-described object. Stents can be radiolabled easily by the disclosed processes and metered precisely. The stents according to the invention are readily physiologically compatible. As it was possible to show in the animal model, the restenosis is significantly inhibited after balloon denudation by implantation of the stent according to the invention.

The special advantage of the stents according to the invention is that the physician can select on the spot a (non-radioactive) stent according to his needs and can then activate the selected stent by the described process. The few substances and solutions that are required for this purpose can be supplied prepared accordingly, so that the corresponding physician need only immerse the uncoated stent in the individual solutions in the specific sequence. The invention thus also relates to those substances, solutions and preparations (kits) that are prepared for the processes according to the invention.

Embodiments:

The following examples are to explain the subject of the invention, without intending that it be limited to these examples.

Example 1a

Coating of a Wiktor stent with 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

50 mg of 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (produced according to DE 43 40 809.5) is dissolved in 1 ml of ethanol. The Wiktor stent (22.82 mg, model 6570, Medtronic) is covered with a layer of the solution that is thus produced. Then, 2 ml of water is added and incubated for 15 minutes in an ultrasound bath. The Wiktor stent is removed and dried.

Example 1b

In-111 Labeling of a Wiktor Stent that is Coated with 1-{3-[N-(2-Methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclo-dodecane

A Wiktor stent that is coated as under Example 1a with 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (produced according to DE 43 40 809.5) is covered with a layer of 2 ml of 0.9% sodium chloride solution. After 37 MBq of indium-

trichloride solution is added, the reaction mixture is put into an ultrasound bath for 15 minutes. The stent is removed, the latter is washed three times with 5 ml of 0.9% sodium chloride solution and dried. The Wiktor stent that is thus labeled carries an activity of 1.49 MBq of In-111.

Example 1c

Y-90 Labeling of a Wiktor Stent that is Coated with 1-{3-[N-(2-Methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclo-dodecane

A Wiktor stent that is coated with 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (produced according to DE 43 40 809.5) as under Example 1a is covered with a layer of 2 ml of 0.9% sodium chloride solution. After 37 MBq of yttrium-90-trichloride solution is added, the reaction mixture is put into an ultrasound bath for 15 minutes. The stent is removed, the latter is washed three times with 5 ml of 0.9% sodium chloride solution and dried. The Wiktor stent that is thus labeled carries an activity of 1.12 MBq of Y-90.

Example 2a

1-{3-[N-(2-Methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane, Y-90 complex

50 mg of 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-

tetraazacyclododecane (produced according to DE 4340809.5) is dissolved in 1 ml of ethanol. After 37 MBq of yttrium-90-trichloride solution is added, the reaction mixture is refluxed for 10 minutes. The Y-90 complex solution that is thus prepared can be used without further purification for coating a Wiktor stent.

Example 2b

Y-90-Labeling of a Wiktor Stent with the Y-90 Complex of 1-{3-[N-(2-Methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclo-dodecane

A Wiktor stent (22.89 mg, model 6570, Medtronic) is added to 900 µl of the solution, produced under Example 2a, of 1-{3-[N-(2-methoxyethyl)-octadecylsulfamoyl]-2-hydroxypropyl}-4,7,10-tris-(hydroxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane-Y-90-complex. After 2 ml of water is added, the reaction mixture is put into an ultrasound bath for 15 minutes. Then, the Wiktor stent is removed and washed three times with 5 ml of 0.9% sodium chloride solution. The Wiktor stent that is thus labeled carries an activity of 0.98 MBq of Y-90.

Example 3a

N,N'-Bisundecyl-diethylene-triamine-pentaacetic acid-diamide

3.57 g (10 mmol) of diethylene-triamine-pentaacetic acid-bisanhydride is suspended together with 4.05 g (40 mmol) of triethylamine in 100 ml of absolute dimethylformamide. Then, a solution of 3.42 g (20 mmol) of undecylamine, dissolved in 50 ml

of absolute dichloromethane, is added in drops to the reaction mixture at room temperature. The reaction batch is stirred for 6 hours at room temperature, filtered and concentrated by evaporation in a medium-high vacuum. The residue is dissolved three times in 100 ml of dimethylformamide and in each case concentrated by evaporation in a medium-high vacuum. 50 ml of absolute diethyl ether is poured over the foamy reaction product and stirred overnight. It is filtered and dried in a medium-high vacuum.

Yield: 6.3 g (90%), white powder.

Elementary analysis:

Cld: C 61.77 H 9.94 N 10.01 O 18.86

Fnd: C 61.52 H 9.63 N 9.91 O

Example 3b

Coating of a Wiktor Stent with N,N'-Bisundecyl-diethylene-triamine-pentaacetic acid-diamide

50 mg of N,N'-bisundecyl-diethylene-triamine-pentaacetic acid-diamide (produced according to Example 3a) is dissolved in 1 ml of ethanol. The Wiktor stent (22.93 mg, model 6570, Medtronic) is covered with a layer of the solution that is thus produced. Then, 2 ml of water is added, and it is incubated for 15 minutes in an ultrasound bath. The Wiktor stent is removed and dried.

Exampl 3c

In-111-Labeling of a Wiktor Stent that is Coated with N,N'-Bisundecyl-diethylene-triamine-pentaacetic acid-diamide

A Wiktor stent that is coated with N,N'-bisundecyl-diethylene-triamine-pentaacetic acid-diamide as under Example 3b is covered with a layer of 2 ml of 0.9% sodium chloride solution. After 37 MBq of indium-trichloride solution is added, the reaction mixture is put into an ultrasound bath for 15 minutes. The stent is removed, the latter is washed three times with 5 ml of 0.9% sodium chloride solution and dried. The Wiktor stent that is thus labeled carries an activity of 1.34 MBq of In-111.

Example 3d

Y-90-Labeling of a Wiktor Stent that is Coated with N,N'-Bisundecyl-diethylene-triamine-pentaacetic Acid-diamide

A Wiktor stent that is coated with N,N'-bisundecyl-diethylene-triamine-pentaacetic acid-diamide as under Example 3b is covered with a layer of 2 ml of 0.9% sodium chloride solution. After 37 MBq of yttrium-trichloride solution is added, the reaction mixture is put into an ultrasound bath for 15 minutes. The stent is removed, the latter is washed three times with 5 ml of 0.9% sodium chloride solution and dried. The Wiktor stent that is thus labeled carries an activity of 1.11 MBq of Y-90.

Example 4a

N,N'-Bisundecyl-diethylene-triamine-pentaacetic Acid-diamide, Y-90 Complex

50 mg of N,N'-bisundecyl-diethylene-triamine-pentaacetic acid-diamide (Example 4a) is dissolved in 1 ml of ethanol. After 37 MBq of yttrium-90-trichloride solution is added, the reaction mixture is heated for 10 minutes to 60°C. The Y-90-complex solution that is thus prepared can be used without further purification for coating a Wiktor stent.

Example 4b

Y-90-Labeling of a Wiktor Stent with the Y-90 Complex of N,N'-Bisundecyl-diethylene-triamine-pentaacetic acid-diamide

A Wiktor stent (22.87 mg, model 6570, Medtronic) is added to 900 µl of the solution, produced under Example 4a, of the Y-90 complex of N,N'-bisundecyl-diethylene-triamine-pentaacetic acid-diamide. After 2 ml of water is added, the reaction mixture is put into an ultrasound bath for 15 minutes. Then, the Wiktor stent is removed and washed three times with 5 ml of 0.9% sodium chloride solution. The Wiktor stent that is thus labeled carries an activity of 0.99 MBq of Y-90.

Example 5a

N-Benzyloxycarbonyl-glycyl-N'-undecyl-glycinamide

3.63 g (10 mmol) of N-benzyloxycarbonyl-glycyl-glycine-N-hydroxysuccinimide ester and 1.71 g (10 mmol) of undecylamine are dissolved in 100 ml of absolute dichloromethane. The reaction

mixture is stirred for 6 hours at room temperature. Then, it is diluted with 100 ml of dichloromethane, the organic phase is washed twice with 50 ml of saturated sodium bicarbonate solution and once with 50 ml of water. It is dried on magnesium sulfate, and the solvent is evaporated in a vacuum. The crude product is purified by chromatography on silica gel (eluant: dichloromethane/methanol 95:5).

Yield: 3.8 g (90.6%), white powder

Elementary analysis: Cld: C 65.84 H 8.89 N 10.01 O 15.25

Fnd: C 65.71 H 9.02 N 10.10 O

Example 5b

Glycyl-N'-undecyl-glycinamide

3 g (7.15 mmol) of N-benzyloxycarbonyl-glycyl-N'-undecyl-glycinamide (Example 5a) is dissolved in 100 ml of absolute ethanol. After 300 mg of palladium is added to carbon (10%), it is hydrogenated for 2 hours at room temperature (1 atmosphere of hydrogen). It is filtered and concentrated by evaporation in a vacuum. The resulting amine is used without further purification for the subsequent reaction.

Yield: 1.92 g (94.1%), white foam.

Elementary analysis: Cld: C 63.12 H 10.95 N 14.72 O 11.21

Fnd: C 63.03 H 11.04 N 14.57 O

Example 5c

N-(S-Acetyl-mercaptoacetyl)-glycyl-N'-undecyl-glycinamide

285.4 mg (1 mmol) of glycyl-N'-undecyl-glycinamide (Example 5b) and 231.2 mg (1 mmol) of S-acetyl-mercapto-acetic acid-N-hydroxy-succinimide ester are dissolved together in 20 ml of absolute dichloromethane. The reaction mixture is stirred for 6 hours at room temperature. Then, it is diluted with 20 ml of dichloromethane, the organic phase is washed twice with 5 ml of semisaturated sodium bicarbonate solution and washed once with 5 ml of water. It is dried on magnesium sulfate, and the solvent is evaporated in a vacuum. The crude product is purified by chromatography on silica gel (eluant: dichloromethane/methanol 93:7).

Yield: 362 mg (90.1%), white powder.

EA:	Cld:	C 56.83	H 8.79	N 10.46	O 15.94	S 7.98
	Fnd:	C 56.67	H 8.93	N 10.18	O	S 7.72

Example 5d

N-(Mercaptoacetyl)-glycyl-N'-undecyl-glycinamide

201 mg (0.5 mmol) of N-(S-acetyl-mercaptoacetyl-glycyl-N'-undecyl-glycinamide (Example 5c) is dissolved in 15 ml of absolute ethanol. It is saturated with argon, and an ammonia stream is directed through the solution for 30 minutes. Then, it is concentrated by evaporation, and the residue is taken up in 20 ml of dichloromethane. The organic phase is shaken once with 2% aqueous citric acid and dried on sodium sulfate. The solvent is

evaporated in a vacuum, and the residue is chromatographed on silica gel (eluant: dichloromethane/methanol 9:1).

Yield: 153 mg (85.1%), white powder.

EA: Cld: C 56.79 H 9.25 N 11.69 O 13.35 S 8.92

Fnd: C 56.67 H 9.43 N 11.48 O S 8.71

Example 5e

Coating of a Wiktor Stent with N-(Mercaptoacetyl)-glycyl-N'-undecyl-glycinamide

50 mg of N-(mercaptoacetyl)-glycyl-N'-undecyl-glycinamide (Example 14d) is dissolved in 1 ml of ethanol. The Wiktor stent (22.89 mg, model 6570, Medtronic) is covered with a layer of the solution that is thus produced. Then, 2 ml of water is added, and it is incubated for 15 minutes in an ultrasound bath. The Wiktor stent is removed and dried.

Example 5f

Re-186-Labeling of a Wiktor Stent that is Coated with N-(Mercaptoacetyl)-glycyl-N'-undecyl-glycinamide

A Wiktor stent that is coated with N-(mercaptoacetyl)-glycyl-N'-undecyl-glycinamide, as under Example 5e, is covered with a layer of 2 ml of disodium hydrogen phosphate buffer (0.1M, pH = 8.5). After 37 MBq of perrhenate solution is added, 100 µl of tin dichloride-dihydrate solution (5 mg of SnCl2x2H2O/1 ml of 0.1M HCl) is added to the reaction batch. The reaction mixture is put into an ultrasound bath for 15 minutes. The stent is removed, the latter is washed three times with 5 ml of 0.9%

sodium chloride solution and dried. The Wiktor stent that is thus labeled carries an activity of 1.31 MBq of Re-186.

Example 5g

N-(Mercaptoacetyl)-glycyl-N'-undecyl-glycinamide, Re-186 Complex

5 mg of N-(mercaptoacetyl)-glycyl-N'-undecyl-glycinamide (Example 5d) is dissolved in 800 µl of ethanol. After 5 mg of disodium-L-tartrate and 50 µl of 0.1M sodium hydrogen phosphate buffer (pH = 8.5) are added, 37 MBq of perrhenate and 100 µl of tin dichloride-dihydrate solution (5 mg of SnCl2x2H2O/1 ml of 0.1M HCl) are added. The reaction mixture is heated for 5 minutes to 60°C. The solution of the Re-186 complex of N-(mercaptoacetyl)-glycyl-N'-undecyl-glycinamide that is thus prepared can be used directly for labeling a Wiktor stent.

Example 5h

Labeling of a Wiktor Stent with the Re-186 Complex of N-(Mercaptoacetyl)-glycyl-N'-undecyl-glycinamide

A Wiktor stent (22.99 mg, model 6570, Medtronic) is added to 900 µl of the solution, produced under Example 5g, of the Re-186 complex of N-(mercaptoacetyl)-glycyl-N'-undecyl-glycinamide. After 2 ml of water is added, the reaction mixture is put into an ultrasound bath for 15 minutes. Then, the Wiktor stent is removed and washed three times with 5 ml of 0.9% sodium chloride solution. The Wiktor stent that is thus labeled carries an activity of 1.13 MBq of Re-186.

Example 6

Y-90-Direct Labeling of a Wiktor Stent

A Wiktor stent (22.85 mg, model 6570, Medtronic) is covered with a layer of 2 ml of saturated sodium oxalate solution. 37 MBq of yttrium-90-trichloride solution is added and heated for 30 minutes to 60°C. Then, the stent is removed and washed three times with 5 ml of 0.9% sodium chloride solution. The Wiktor stent that is thus labeled carries an activity of 0.88 MBq of Y-90.

Example 7

Use of Bisdecyloylhydrazino-diethylenetriamine-pentaacetate for Coating Stents

Example 7a

Production of Bisdecyloylhydrazino-diethylenetriamine-pentaacetate:

17.5 g of decanoic acid methyl ester is dissolved in 1 l of absolute ethanol and mixed with 350 ml of hydrazine hydrate. It is refluxed for 3 hours and then stirred overnight at room temperature. The solution is concentrated by evaporation to about 300 ml and allowed to stand until the product is crystallized out. After it is filtered off and dried, 16.6 g (= 94% of theory) of decanoic acid hydrazide is obtained.

Elementary analysis:	C	H	N	O
Calculated:	64.5%	11.9%	15.0%	8.6%
Found:	65.4%	11.9%	14.5%	

3.6 g of diethylenetriamine-pentaacetic acid-bisanhydride is dissolved in 500 ml of DMF and mixed under nitrogen atmosphere with 4.2 ml of triethylamine and 3.7 g of decanoic acid hydrazide. It is stirred for 24 hours at room temperature and then undissolved components are filtered off. The solution is concentrated by evaporation, and the oily residue is taken up in 500 ml of ether. After 500 ml of hexane is added and stirring is continued, the product precipitates in crystalline form. After drying, 7.2 g (= 95% of theory) of bisdecyloylhydrazino-diethylene-triamine-pentaacetate is obtained.

Example 7b

Coating of Strecker Stents with Bisdecyloylhydrazino-diethylenetriamine-pentaacetate

2 mg of bisdecyloylhydrazino-diethylenetriamine-pentaacetate is dissolved in 1 ml of methanol and precipitated with the addition of 2 ml of hexane. In this suspension, a Strecker stent 0.5 cm in length (SS/5-4, Boston Scientific) is immersed and incubated for 15 minutes by means of ultrasound. The stent is then taken out and dried. This process was repeated five times, and finally excess coating material was removed by washing with physiological common salt solution in an ultrasound bath.

Example 7c

Labeling of Strecker Stents that are Coated with Bisdecyloylhydrazino-diethylenetriamine-pentaacetate

The thus treated stent was immersed for labeling in a commercially acquired solution of the radioactive metal isotope (In-111, Y-90, 74 MBq each) and incubated for 15 minutes in an ultrasound bath. Finally, it was washed in physiological saline for 20 minutes in an ultrasound bath. 0.3 MBq of residual activity remains on the stent.

Example 7d

Coating of Strecker Stents with Labeled Bisdecyloylhydrazino-diethylenetriamine-pentaacetate

2 mg of bisdecyloylhydrazino-diethylenetriamine-pentaacetate is dissolved in 1 ml of methanol and labeled with a commercially acquired solution of the radioactive metal isotope (In-111, Y-90, 74 MBq each). In this solution, a Strecker stent 0.5 cm in length (SS/5-4, Boston Scientific) is immersed and incubated for 15 minutes by means of ultrasound. Then, the stent was taken out and dried. This process was repeated 5 times, and finally soluble activity was removed by washing with physiological common salt solution in an ultrasound bath. 0.1 MBq of residual activity remains on the stent.

Exampl 8

Use of Thioacetyl-Gly-Gly-amidoethyl-PEG-methylether for Coating Stents

Production of Thioacetyl-Gly-Gly-amidoethyl-PEG-methylether:

50 g of aminoethyl-polyethyleneglycol-methylether with a molecular weight of about 5000 is stirred with 3.6 g of N-benzyloxycarbonyl-glycylglycine-N-hydroxysuccinimide ester (Z-Gly-Gly-OSu) in 100 ml of DMF for 24 hours at room temperature. The solution is concentrated by evaporation, and the residue is further reacted without further purification.

The residue is dissolved in a mixture of methanol/water 1:1, mixed with 2 g of palladium on activated carbon and hydrogenated under hydrogen atmosphere (pressure 1 bar) until about 230 ml of hydrogen is taken up. Then, the catalyst is filtered off, and the remaining mixture is purified after concentration by evaporation with a gel filtration. After drying, 49 g (= 96% of theory) of glycyl-glycyl-amidoethyl-PEG-methylether is obtained.

This product is dissolved in 100 ml of DMF and stirred with 2.2 g of S-acetyl-thioglycolic acid-N-hydroxysuccinimide ester for 24 hours at room temperature. Then, the mixture is mixed with 20 ml of aqueous ammonia solution and stirred for 2 more hours. The product is acidified to pH 4 with aqueous 6N hydrochloric acid and concentrated by evaporation. The purification is carried out on a gel filtration column. 42 g (= 85% of theory) of thioacetyl-glycyl-glycyl-amidoethyl-polyethyleneglycol-methyl ester is obtained.

Example 8b

Coating of Strecker Stents with Thioacetyl-Gly-Gly-amidoethyl-PEG-methylether and Subsequent Radiolabeling

a) 2 mg of thioacetyl-Gly-Gly-amidoethyl-PEG-methylether with a molecular weight of about 5300 was dissolved in 2 ml of methanol, precipitated with the addition of 1 ml of hexane, a Strecker stent 0.5 cm in length (SS/5-4, Boston Scientific) was immersed in this suspension and incubated by means of ultrasound for 15 minutes. Then, the stent was taken out and dried. This process was repeated five times, and finally excess coating material was removed by washing with physiological common salt solution in an ultrasound bath.

The thus treated stent was immersed for labeling in a solution of the radioactive metal isotope (Tc-99m, Re-186) that consists of 5 ml of the solution (Tc-99m from the generator, Re-186 that was acquired commercially and contained about 3 MBq of activity), 200 µl of phosphate buffer (Na_2HPO_4, 0.5 mol/l, pH 8.5), 50 µl of a 0.15 molar disodium tartrate solution and 2.5 µl of a 0.2 molar $SnCl_2$ solution and incubated for 15 minutes in an ultrasound bath. Finally, it was washed in physiological salin for 20 minutes in an ultrasound bath. 0.1 MBq of residual activity remains on the stent.

Example 8c

Coating of Strecker Stents with Radiolabeled Thioacetyl-Gly-Gly-amidoethyl-PEG-methylether

0.5 mg of thioacetyl-Gly-Gly-amidoethyl-PEG-methylether with a molecular weight of about 5300 was dissolved in 300 µl of phosphate buffer (Na_2HPO_4, 0.5 mol/l, pH 8.5), and 50 µl of a 0.15 molar disodium tartrate solution and 2.5 µl of a 0.2 molar $SnCl_2$ solution were added. The mixture was mixed with a pertechnetate solution (2 MBq) from a Tc-99m generator and incubated for 15 minutes at 60°C. A solution of polyethylene glycols that are labeled with Re-186 could be produced analogously.

A Strecker stent 0.5 cm in length (SS/5-4, Boston Scientific) was immersed in this solution and incubated for 15 minutes by means of ultrasound. Then, the stent was taken out and dried. This process was repeated several times in succession, until the adhering activity had reached 0.3 MBq. Then, it was washed twice for 60 minutes in physiological saline. A residual activity of 100 KBq remained.

Example 9

Coating of Strecker Stents with Tc-99m-Asp-Gly-Gly-Cys-Gly-Cys-Phe-(Dr-Trp)-Leu-Asp-Ile-Ile-Trp

0.5 mg of the Asp-Gly-Gly-Cys-Gly-Cys-Phe-(D-Trp)-Leu-Asp-Ile-Ile-Trp that was produced analogously to Barany and Marrifield, The Peptides; Analysis, Biology, Academic Press, New York, 1990; Stewart and Young, Solid-Phase Peptide Synthesis, 2nd

Edition, Pierce Chemical Co., Rockford, IL, 1984 is dissolved in 300 ml of phosphate buffer (Na_2HPO_4, 0.5 mol/l, pH 8.5) and mixed with 50 µl of a 0.15 molar disodium-L-tartrate solution, 2.5 µl, of a 0.2 molar tin(II) chloride-dihydrate solution. The reaction mixture is mixed with a pertechnetate solution (50 mCi = 1.85 GBq) from an Mo-99/Tc-99m-generator and incubated for 10 minutes at room temperature.

A Strecker stent 0.5 cm in length (SS/5-4, Boston Scientific) was incubated five times in succession for 15 minutes each in the Tc-99m-peptide solution. After each incubation, the activity that adheres to the stent was determined with the aid of a commercially available gamma counter. As the figure shows, an activity of 230 µCi on the Strecker stent remained even after one-time incubation.

The repetitions of this incubation do not result in any significantly higher activity that remains on the stent. The stent that was coated with the Tc-99m-peptide solution was then washed four times every minute and twice for 60 minutes in physiological saline. After the first rinsing, 81 µCi still remains on the stent. The additional rinsing processes did not result in any significant reduction of the activity that is bonded to the stent.

Example 10

Tc-99m-Coating of Strecker Stents

A Wiktor stent (22.92 mg, model 6570, Medtronic) is covered with a layer of 2.56 ml of sodium-pertechnetate solution (911.5

MBq). 256 µl of tin(II) chloride-dihydrate solution (5 mg of $SnCl_2 \cdot 2H_2O$/1 ml of 0.01 M HCl) is add d, the reaction mixture is put into an ultrasound bath for 5 minutes and finally incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 2.56 ml of 0.9% sodium chloride solution. Finally, it is again covered with a layer of 2.56 ml of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Wiktor stent carries an activity of 5.9 MBq-Tc-99m/22.92 mg (≙ 159.5 µCi/22.92 mg ≙ 6.9 µCi/1 mg).

Example 11

Re-186 Coating of Wiktor Stents

A Wiktor stent (22.31 mg, model 6570, Medtronic) is covered with a layer of 2.5 ml of sodium pertechnetate solution (884.1 MBq). 249 µl of tin(II) chloride-dihydrate solution (5 mg of SnCl2 $\cdot 2H_2O$/1 ml of 0.01 M HCl) is added, the reaction mixture is put into an ultrasound bath for 5 minutes and finally incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 2.5 ml of 0.9% sodium chloride solution. Finally, it is again covered with a layer of 2.5 ml of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Wiktor stent carries an activity of 5.2 MBq-Re-186/22.31 mg (≙ 140.5 µCi/22.31 mg ≙ 6.3 µCi/1 mg).

Example 12

Administration of a Wiktor Stent that is Coated with Tc-99m in the Abdominal Aorta of Rabbits

The Wiktor stent (model 6570, Medtronic) was coated with Tc-99m as described in Example 10. In an anesthetized (Rompun/Ketavet 1:2) white New Zealand rabbit (3.2 kg of body weight), the femoral artery was exposed. The labeled Wiktor stent was inserted into the vessel via a 5 F sluice and secured in the infrarenal aorta by inflating the balloon catheter. The catheter was then removed, and both the femoral artery and the wound were sutured. Over a period of 8 hours after administration of the stent, whole-body scintigrams were prepared with the aid of a commercially available gamma camera. Figure XI shows a scintigram that was prepared five hours after administration of the stent. Activity could only be located in the area of the stent that is in the infrarenal aorta of the animal. During the entire examination period, no detectable activity was rinsed from the stent. After 8 hours, the rabbit was killed, the stent was removed, and the activity was measured in a gamma counter. The activity that adheres to the stent was equally as high as at the beginning of the test.

Example 13a

Cementation of a Strecker Stent with Gold

A Strecker stent (about 200 mg) is coated with gold (2 minutes of 30 mg of gold(III)-chloride in 30 ml of 5% aqueous hydrochloric acid) in a cementation vessel (Fig. 2a). The stent

that is thus obtained is washed three times with 10% aqueous nitric acid and twice with water. Then, it is [washed] twice with acetonitrile and dried.

Example 13b

Linkage of 11-Amino-undecyl-1-thiol to the Surface

500 mg of 11-aminoundecyl-1-thiol is dissolved in a solution that consists of 10 ml of 7.5% aqueous nitric acid/5 ml of tetrahydrofuran/3 ml of 1,2-dichloromethane. The Strecker stent that is produced from Example 13a is immersed in this solution under protective gas (in an ultrasound bath/37°C). It is irradiated for about 15 minutes. The stent is washed three times with ethanol, then twice with acetonitrile.

Example 13c

Coupling with DTPA-bis-anhydride

The stent that is described in Example 13b is immersed in a 7.5% aqueous sodium carbonate solution, and 500 mg of DTPA-bis-anhydride in 5 portions per 100 mg each is added at 0°C while being stirred. It is stirred for 10 minutes at 0°C. The stent is washed twice with 5% aqueous hydrochloric acid, then three times with water and twice with acetonitrile.

Example 13d

Indium-111-Labeling of the Stent that is Derivatized from DTPA-Amide

The stent that is described in Example 13c is immersed in a solution of acetate buffer (0.001 mol, pH 5.5), and In-111 solution (starting activity: 48.8 MBq) is added. It is stirred for 5 minutes at room temperature. The stent is washed three times with 3% aqueous sodium carbonate solution, then twice with physiological common salt solution. The stent can be used directly for implantation. The stent showed a radioactivity of 1.2 MBq.

Example 14a

Coupling of DOTA to the Stent of Example 13b

The stent that is obtained from Example 13b is immersed in a solution of phosphate buffer (0.1 mol/l, pH 7.4), and 150 mg of 1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DOTA) is added. It is cooled to 0°C, and 200 mg of N-hydroxysulfosuccinimide (Sulfo-NHS) and 200 mg of 1-ethyl-3-(dimethylaminopropyl)-carbodiimide HCl (EDC) are added. It is stirred for 30 minutes at 0°C. The stent is washed twice with water and twice with physiological common salt solution.

Example 14b

Labeling with In-111

The stent that is described in Example 14a is immersed in a solution of acetate buffer (0.01 mol, pH 5), and In-111 solution

(starting activity: 37.3 MBq) is add d. It is heated for 30 minutes to 50°C. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 1.45 MBq.

Example 15a

Coupling of 4-Isothiocyanato-benzyl-DTPA to the Stent of Example 13b

A stent that is prepared in Example 13b is immersed in a solution of sodium carbonate buffer (0.1 mol/l, pH 9), and 100 mg of 4-isothiocyanato-benzyl-DTPA (Gansow, O. WO 91/14459) is added. It is stirred for 30 minutes at room temperature. The stent is washed twice with 3% sodium carbonate solution, then three times with physiological common salt solution.

Example 15b

Labeling with Cu-67

The stent that is described in Example 15a is immersed in a solution of acetate buffer (0.01 mol, pH 5), and Cu-67 solution (starting activity: 34.5 MBq) is added. It is stirred for 5 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 0.98 MBq.

Example 16a

Coupling of 4-Isothiocyanato-benzyl-DOTA to the Stent of Example 13b

A stent that is prepared in Example 13b is immersed in a solution of sodium carbonate buffer (0.1 mol/l, pH 9), and 100 mg of 4-isothiocyanato-benzyl-DOTA (Gansow, O. US 4,923,985) is added. It is stirred for 30 minutes at room temperature. The stent is washed twice with 3% sodium carbonate solution, then three times with physiological common salt solution.

Example 16b

Labeling with Cu-67

The stent that is described in Example 16a is immersed in a solution of acetate buffer (0.01 mol, pH 5), and Cu-67 solution (starting activity: 28.6 MBq) is added. It is stirred for 15 minutes at 40°C. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 0.77 MBq.

Example 17a

Bisamide of Cystamine with DTPA

10 g (28 mmol) of DTPA-bis-anhydride is suspended in 100 ml of dimethyl sulfoxide. It is cooled to 0°C, and 5.7 g (56 mmol) of triethylamine is added. Then, 1.58 g (7 mmol) of cystamine dihydrochloride is added, and it is stirred for 24 hours at room temperature. 20 ml of formic acid and 1000 ml of diethyl ether

are added. The precipitated solid is filtered off and chromatographed on RP18 (mobile solvent: gradient that consists of acetonitrile/THF/water). The product that is obtained after the main fractions are concentrated by evaporation is recrystallized from a little methanol.

Yield: 1.96 g (31% of theory relative to cystamine) of a colorless, hygroscopic solid.

Water Content: 6.8%

Elementary analysis (relative to anhydrous substance):

Cld: C 42.57 H 6.03 N 12.41 S 7.10

Fnd: C 42.39 H 5.97 N 12.53 S 7.03

Example 17b

Coupling of DTPA-Cysteamine Amide to a Gold-Cemented Strecker Stent (13a)

The Strecker stent that is described in Example 13a is fixed in an electrolysis cell (Fig. 1), and a solution of phosphate buffer (0.1 mol/l, pH 5) is added. 100 mg of the title compound of Example 126a is added to the solution, and a voltage of 3 V is applied. Electrolysis is done for 15 minutes at room temperature. The stent is washed four times with water and can be used directly for labeling.

Example 17c

Labeling with In-111

The stent that is described in Example 17b is immersed in a solution of acetate buffer (0.01 mol, pH 5), and In-111 solution

(starting activity: 34.7 MBq) is added. It is stirred for 5 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 1.11 MBq.

Example 18

Labeling with Cu-67

The stent that is described in Example 17b is immersed in a solution of acetate buffer (0.01 mol, pH 5), and Cu-67 solution (starting activity: 41.2 MBq) is added. It is stirred for 3 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 0.97 MBq.

Example 19a

Coupling of N,N-dimethyl-2-(3,3,5,11,13,13-hexamethyl-1,2-dithia-5,8,11-triaza-cyclotridecan-8-yl)-ethylamine to a Gold-Cemented Strecker Stent

The Strecker stent that is described in Example 13a is fixed in an electrolysis cell (Fig. 1), and a solution of phosphate buffer (0.1 mol/l, pH 5) is added. 100 mg of N,N-dimethyl-2-(3,3,5,11,13,13-hexamethyl-1,2-dithia-5,8,11-triaza-cyclotridecan-8-yl)-ethylamine (produced according to WO 96/11918, Example 27) is added to the solution, and a voltage of 3.5 V is applied. Electrolysis is done for 15 minutes at room

temperature. The stent is washed four times with water and can be used directly for labeling.

Example 19b

Labeling with Re-186

The stent that is described in Example 19a is immersed in a solution that consists of 30 ml of acetate buffer (0.01 mol, pH 5 and 100 mg of tin(II)-chloride), and Re-186 solution (starting activity: 48.3 MBq) is added. It is stirred for 3 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, then three times with physiological common salt solution. The stent showed a radioactivity of 1.44 MBq.

Example 20

Labeling of a Gold-Cemented Stent with In-111 With In-situ Coupling of the Title Compound of Example 17a Using Electrochemical Reduction

The Strecker stent that is described in Example 13a is fixed in an electrolysis cell (Fig. 1), and a solution of phosphate buffer (0.1 mol/l, pH 5) is added. 10 mg of the title compound of Example 17a, In-111 solution (starting activity: 34.6 MBq) is added to the solution, and a voltage of 3 V is applied. Electrolysis is done for 15 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, twice with water and can be implanted directly. The stent showed a radioactivity of 0.77 MBq.

Example 21

Labeling of a Gold-Cemented Stent with Cu-67 with In-situ Coupling of the Title Compound of Example 17a Electrochemical Reduction

The Strecker stent that is described in Example 13a is fixed in an electrolysis cell (Fig. 1), and a solution of citric acid buffer (0.1 mol/l, pH 5) is added. 10 mg of the title compound of Example 17a, Cu-67 solution (starting activity: 36.7 MBq), is added to the solution, and a voltage of 1.8 V is applied. Electrolysis is done for 15 minutes at room temperature. The stent is washed twice with 3% aqueous sodium carbonate solution, twice with water and can be implanted directly. The stent showed a radioactivity of 0.98 MBq.

Example 22

Labeling with S-35

A stent that is produced according to 13a is put into a solution that consists of 5% aqueous hydrochloric acid, and a solution of S-35-cysteine (initial activity 37.5 MBq) is added. It is stirred for 5 minutes at room temperature. The stent is washed four times with physiological common salt solution. A radioactivity of 1.35 MBq is measured.

Claims

1. Radioactive stents, characterized in that the radioactive isotope is fixed on the surface of the stent by means of at least one adhesive.

2. Radioactive stents, wherein at least one radioactive isotope of elements Ag, Au, Ba, Bi, C, Co, Cr, Cu, Fe, Gd, Hg, Ho, In, Ir, Lu, Mn, Ni, P, Pb, Pd, Pm, Pt, Re, Rh, Ru, S, Sb, Sc, Sm, Tb, Tc or Y is fixed on the surface of the stent by means of at least one adhesive.

3. Radioactive stents according to claim 1 or 2, wherein the adhesive consists of a peptide, a fat or gold in combination with a thiol-group-containing complexing agent.

4. Radioactive stents according to claim 1 or 2, wherein the adhesive consists of a complexing peptide, a complexing fat or gold in combination with a thiol group-containing complexing agent.

5. Radioactive stents according to claim 1, wherein the radioactive isotope is an isotope of elements Ag, Au, Ba, Bi, C, Co, Cr, Cu, Fe, Gd, Hg, Ho, In, Ir, Lu, Mn, Ni, P, Pb, Pd, Pm, Pt, Re, Rh, Ru, S, Sb, Sc, Sm, Tb, Tc or Y.

6. Process for the production of radioactive stents, wherein a radioactive isotope is reacted with an adhesive at 0-100°C, and the stent is then coated with the radiolabeled adhesive at 0°C-100°C.

7. Process for the production of radioactive stents, wherein a non-radioactive stent is coated with the adhesive at

0°C-100°C, and then is mixed at 0-100°C with a solution of the radioactive isotope.

8. Process for the production of radioactive stents, wherein a non-radioactive stent is coated with gold and then is mixed at 0-100°C with a solution of a ^{35}S-labeled thiol compound.

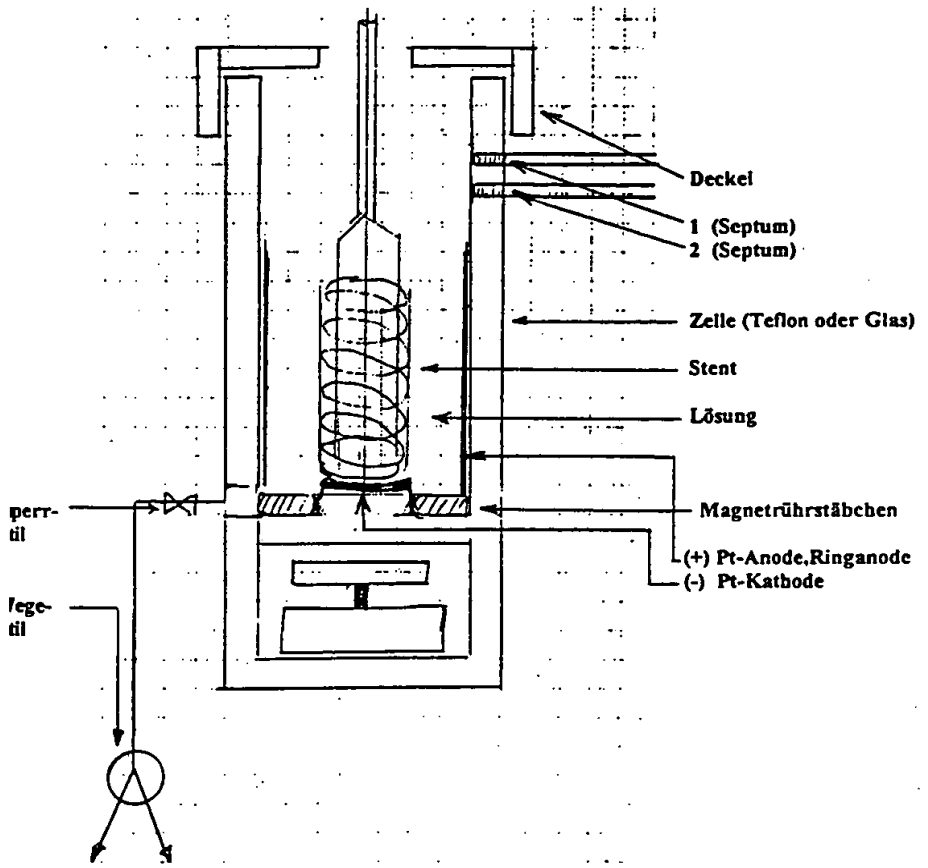
9. Use of stents that consist of stent parent substances, adhesives and a radioactive isotope for the production of an implant for prophylaxis of restenoses.

Stents with a Radioactive Coating, Processes for their Production and their Use for Restenosis Prophylaxis

Abstract

The invention relates to stents that are radioactively coated on the surface by means of adhesives, processes for their production and their use for restenosis prophylaxis.

Galvanization Cell (Fig. 1)



Addition of solutions: Hypodermic syringes or metering pumps

When addition is done with hypodermic syringes: Put septa in the cover.

If electrolysis is carried out at an elevated temperatur , the solution is preheated.

1: Rinsing liquid

2: Active solution

[Key:]

Deckel = cover

Septum = septum

Zelle (Teflon oder Glas) = cell (teflon or glass)

Stent = stent

Lösung = solution

Absperrventil = shutoff valve

2-Wege-ventil = 2-way valve

Magnetrührstäbchen = magnetic stirring rod

(+) Pt-anode, Ringanode = (+) Pt-anode, ring anode

(-) Pt-Kathode = (-) Pt-cathode